

sequence that is at least 80% identical to any one of SEQ ID NOs: 1-7, 149-164, 333-337, and 384 and/or a  $V_L$  Comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 8-13, 148, 338-343, and 385. For example, the antibody, or fragment or variant thereof, may comprise: a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 6 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 12; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 7 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 13; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 333 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 338; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 334 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 339; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 335 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 340; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 336 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 341; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 337 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 342; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 335 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 343; a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 384 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 385; or a  $V_H$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 386 and a  $V_L$  Comprising a sequence that is at least 90% identical to SEQ ID NO: 387.

**[0017]** In certain embodiments, the anti-PD-1 antibody, or fragment or variant thereof, is: AM-0001; AMP-224; balstilimab; budigalimab; BI 754091; camrelizumab; cemiplimab; cetrelimab; dostarlinab; JTX-4014; MEDI-0680; MGA012; nivolumab; pembrolizumab; pidilizumab; prolgolimab; sasanlimab; sintilimab; spartalizumab; STI-1110; tislelizumab; toripalimab; or zimberelimab; or a fragment or variant thereof. For example, the anti-PD-1 antibody, or fragment or variant thereof, is: pembrolizumab; nivolumab; zimberelimab; or cetrelimab; or a fragment or variant thereof. In certain embodiments, the anti-PD-1 antibody, or fragment or variant thereof, of the first component is cetrelimab, or a fragment or variant thereof.

**[0018]** In certain embodiments, the anti-PD-1 antibody, or fragment or variant thereof, comprises a sequence that is at least 90% identical to SEQ ID NO: 15 and a sequence that is at least 90% identical to SEQ ID NO: 16 or 143. In certain embodiments, the anti-PD-1 antibody, or fragment or variant thereof, comprises a sequence that is at least 80% identical to SEQ ID NO: 296 and a sequence that is at least 80% identical to any one of SEQ ID NOs: 144, 145, and 295. In certain embodiments, the anti-PD-1 antibody, or fragment or variant thereof, comprises a sequence that is at least 80% identical to SEQ ID NO: 13 or 15 and a sequence that is at least 80% identical to SEQ ID NO: 294 or 295.

**[0019]** In certain embodiments, the second component of the fusion protein is a cytokine trap, for example a TGF- $\beta$  cytokine trap. The TGF- $\beta$  cytokine trap may, for example, comprise: a transforming growth factor receptor (TGF $\beta$ R) or a fragment or variant thereof; an anti-TGF- $\beta$  antibody or an antigen binding fragment or variant thereof; a TGF- $\beta$  inhibi-

tory peptide or a fragment or variant thereof; and/or a TGF- $\beta$  antagonistic peptide or a fragment or variant thereof.

**[0020]** In certain embodiments, the TGF- $\beta$  cytokine trap comprises a transforming growth factor beta receptor II (TGF $\beta$ RII) or a fragment or variant thereof.

**[0021]** In certain embodiments, the TGF- $\beta$  cytokine trap comprises a TGF $\beta$ R extracellular domain or a fragment or variant thereof. In certain embodiments, the TGF- $\beta$  cytokine trap comprises a TGF $\beta$ RII extracellular domain, or a fragment or variant thereof, for example comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 14, 141, and 142. In certain embodiments, the TGF $\beta$ RII extracellular domain, or a fragment or variant thereof, binds TGF- $\beta$ 1 and/or TGF- $\beta$ 3. In certain embodiments, the TGF $\beta$ RII extracellular domain, or a fragment or variant thereof, binds TGF- $\beta$ 1 and TGF- $\beta$ 3 but does not bind TGF- $\beta$ 2 or binds TGF- $\beta$ 2 at a lower affinity than it does TGF- $\beta$ 1 and TGF- $\beta$ 3.

**[0022]** In certain embodiments, the TGF- $\beta$  cytokine trap comprises a sequence that is at least 80% identical to any one of SEQ ID NOs: 14, 141, and 142.

**[0023]** In certain embodiments, the TGF- $\beta$  cytokine trap comprises an anti-TGF- $\beta$  antibody or an antigen binding fragment or variant thereof. The antibody, or antigen binding fragment or variant thereof, may for example comprise a variable region of a heavy chain ( $V_H$ ) and a variable region of a light chain ( $V_L$ ). In certain embodiments, the antibody, or antigen binding fragment or variant thereof, may comprise a  $V_H$  comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 166, 168, 169, 171, 173, and 175 and/or a  $V_L$  comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 165, 167, 170, 172, 174, 176, and 178.

**[0024]** In certain embodiments, the TGF- $\beta$  cytokine trap comprises a TGF- $\beta$  inhibitory peptide or a fragment or variant thereof, for example comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 468-507 and 263-267. In certain embodiments, the TGF- $\beta$  cytokine trap comprises two or more TGF- $\beta$  inhibitory peptides, or fragments or variants thereof. The two or more TGF- $\beta$  inhibitory peptides, or fragments or variants thereof, may be connected by linker(s).

**[0025]** In certain embodiments, the TGF- $\beta$  cytokine trap comprises a TGF- $\beta$  antagonistic peptide or a fragment or variant thereof. In certain embodiments, the TGF- $\beta$  cytokine trap comprising two or more TGF- $\beta$  antagonistic peptides, or a fragments or variants thereof. The two or more TGF- $\beta$  antagonistic peptides, or fragments or variants thereof, may be connected by linker(s).

**[0026]** In certain embodiments, the second component of the fusion protein is an ADA or a fragment or variant thereof.

**[0027]** In certain embodiments, the ADA, or fragment or variant thereof, is adenosine deaminase 2 (ADA2) or a fragment or variant thereof, for example one comprising a sequence that is at least 80% identical to any one of SEQ ID NOs: 273-279 and 284. In certain embodiments, the ADA2, or fragment or variant thereof, comprises at least one amino acid substitution or deletion.

**[0028]** In certain embodiments, the first and second components are connected by a linker. The linker may, for example, comprise: (G4S) $_n$ , wherein n is 2, 3, 4, 5, or 6; (Gly) $_n$ , wherein n is 6, 7, or 8; (EAAAK) $_n$ , wherein n is 1, 2, 3, 4, 5, or 6; A(EAAAK) $_4$ ALEA(EAAAK) $_4$ A; and/or a sequence of any one of SEQ ID NOs: 17-34.